The use of left ventricular end-ejection pressure and peak pressure in the estimation of the end-systolic pressure-volume relationship

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ABSTRACT The end-systolic pressure-volume relationship (ESPVR) as derived from left ventricular pressure-volume loops has gained increasing acceptance as an index of ventricular contractile function. In animal experiments the ESPVR has been defined as a line connecting the upper left corners of several differently loaded pressure-volume (P-V) loops with a slope parameter Ees and a volume axis intercept parameter \( V_o \). In the clinical setting, several variants of the ESPVR have been determined with use of peak left ventricular pressure, end-ejection pressure, and end-ejection volume. The maximum P-V ratio has also frequently been measured. We attempted to determine which of these alternatives resulted in good approximations of the reference ESPVR in eight isolated canine ventricles that ejected into a simulated arterial impedance system with resistance, compliance, and characteristic impedance. We determined various versions of the ESPVR from the same set of beats quickly obtained with little change in inotropic background. To vary ventricular pressure wave forms, each of the arterial impedance parameters was independently controlled at 50%, 100%, and 200% of normal. Against each of the nine combinations of the impedance parameters four P-V loops were obtained under normal preload and from each of the sets of four P-V loops, the reference ESPVR, linear regression of the peak pressure on end-ejection volume (ESPVR\(_{PP-EEV}\)), and linear regression of end-ejection pressure on end-ejection volume (ESPVR\(_{EPV-EEV}\)) were determined. In addition, the maximum P-V ratio (MPVR) was calculated for each P-V loop. At all combinations of afterload impedance parameters ESPVR\(_{PP-EEV}\) was shifted to the left (slope 5.4 vs 5.2 mm Hg/ml, intercept 6.6 vs 7.4 ml) and ESPVR\(_{EPV-EEV}\) was shifted rightward (slope 5.0 mm Hg/ml, intercept 7.7 ml) from ESPVR\(_{REF}\). These differences, however, were quantitatively very small. MPVR was much smaller than the slope of ESPVR\(_{REF}\) (4.0 vs 5.2 mm Hg/ml) and was load dependent. We conclude that as long as the P-V measurements are made under a fixed afterload system and different preloads, ESPVR\(_{PP-EEV}\) and ESPVR\(_{EPV-EEV}\), but not MPVR, can be used to approximate ESPVR\(_{REF}\).


THE USE OF the end-systolic pressure-volume relationship (ESPVR) as a clinical index of cardiac ventricular contractile function is being explored.\(^1\) In our laboratory the ESPVR is considered to represent the peak systolic activity of the ventricle in terms of the maximum ratio of ventricular pressure to ventricular volume (MPVR) with allowance for a finite volume (\( V_o \)). It can be determined from several differently loaded beats.\(^2\) The slope and volume intercept parameters of the ESPVR can index ventricular contractile state since they have been found to be relatively insensitive to changes in preload\(^3\-\(^5\) and afterload\(^2\-\(^5\) yet are sensitive to changes in the contractile state of the ventricle.\(^3\-\(^5\)

To facilitate clinical application of the ESPVR in the estimation of ventricular contractility, variants of the ESPVR have been used.\(^1\) There are potential problems with some of these variants. End-systole, by our definition, does not necessarily coincide with end of ejection.\(^2\-\(^6\) Some investigators have assumed \( V_o = 0 \) and used the MPVR,\(^8\) whereas others have used the slope of the regression of peak pressure (or stress) on end-ejection volume ESPVR\(_{PP-EEV}\)\(^8\)-\(^12\) or the slope of the
regression of end-ejection pressure (or stress) on end-ejection volume.\textsuperscript{13-16} Figure 1 illustrates the differences between these points in the cardiac cycle. Figure 1, \textit{top}, shows pressure and volume as a function of time and the \textit{bottom} shows the pressure-volume (P-V) loop. Point A represents the pressure and volume at peak systolic pressure, point C the pressure and volume at end-ejection defined by dV/dt = 0, and point B the pressure and volume at end-systole when the ventricular volume elastance becomes maximum.\textsuperscript{5}

There are reasons for concern as to the validity of these variants of ESPVR. Major variations in the pattern of ventricular ejection and therefore systolic volume may result from alterations in the afterload to the ventricle. How these variations affect the slope and volume intercept parameters of the variants of ESPVR has not been systematically studied.

We determined, from identical beats, ESPVR\textsubscript{PP-EV}, ESPVR\textsubscript{EEPV}, and MPVR assuming a zero volume intercept and compared these variants of ESPVR against a reference ESPVR that was determined as explained in Methods.

In the comparative studies, we evaluated the slope and volume intercept parameters of these alternative methods of measurement of ESPVR and the influence of changing afterload conditions on them. These studies were conducted under nearly optimal conditions. First, we used an isolated supported left ventricular preparation in which the inotropic state was stable. Second, volume determination for the left ventricle in this preparation is known to be extremely accurate at all points in time during the cardiac cycle\textsuperscript{17} and pressure was measured with a micromanometer in the ventricular lumen. Third, we could make all necessary measurements for all methods of determination during the same set of beats. Finally, using a computer-simulated physiologic loading system for the isolated canine heart,\textsuperscript{18} we could independently alter the preload and the afterload impedance, which was based on a three-element Windkessel model.

\textbf{Methods}

\textbf{Surgical preparation.} The supported isolated canine heart preparation has been previously described by Suga et al.\textsuperscript{4} Briefly, we used eight pairs of dogs (20 to 25 kg). Both dogs were anesthetized with sodium pentobarbital (25 mg/kg iv) and ventilated. Flow of oxygenated blood from the support dog to the isolated heart was servocontrolled (Harvard Pump Model 1215) to maintain 80 mm Hg pressure in the aortic root, and the blood was warmed (37\degree C) and filtered. The venous blood was returned to the support animal. A disk oxygenator (Pemco model 7104) in parallel with the support dog was used during the isolation of the heart and as backup for the support dog.

The ventricles of each dog were vented and the chordae tendineae were severed. A metal ring was sutured to the mitral anulus. A water-filled latex balloon connected to a servocontrolled piston pump was placed within the left ventricle through the metal ring. By this method, the error in the measurement of ventricular lumen volume at end-systole is about 0.5 ml.\textsuperscript{17}

\textbf{Servopump hardware.} Details of the ventricular volume control pump system design and performance have previously been reported.\textsuperscript{19} Briefly, a linear motor (Ling Electronics model 411) controlled the piston position of a cylinder pump (Bellofram SS-4-F-SM-UM). The ventricular balloon was connected to this pump. The pump cylinder, connecting tube, and the balloon were all filled with water. A linear displacement transducer (Trans-Tek model 244-000) sensed the piston position producing a signal proportional to the balloon volume. The signal was used in a negative feedback loop for comparison with a volume-command signal (see below) that represented the desired instantaneous volume. The error signal resulting from this comparison was supplied to a power amplifier (Crown model DC-300), which in turn drove the linear motor to minimize error.

\textbf{Impedance loading system.} The ventricular volume command signal for the volume control servosystem was generated by the interaction between the instantaneous pressure in the real ventricle and a hybrid computer that simulated arterial input impedance.\textsuperscript{18} The left ventricular pressure, measured by a pressure transducer (Konigsberg P-21) placed inside the balloon, served as the input to an analog computer (Comdyna 808 Analog Signal Processor) that was programmed to solve differential equations for both the ventricular preloading and afterloading circuit.

![Figure 1](https://circ.ahajournals.org/)

**FIGURE 1.** Oscilloscopic tracings of pressure and volume vs time (\textit{top}) and pressure vs volume (\textit{bottom}) to illustrate the difference between the time of peak pressure (point A in both panels), end-ejection pressure and volume (point C in both panels), and "end-systolic" pressure and volume (point B in both panels). End-systole is defined as the time of maximum chamber stiffness (see text).
The ventricular afterload system was a three-element Windkessel model of the aortic hydraulic input impedance. Flow began when ventricular pressure exceeded that in the simulated artery. The computer calculated ventricular outflow by dividing the pressure difference between the measured left ventricular pressure and aortic pressure by the characteristic impedance. Both the filling and ejecting flow signals were continuously integrated by the analog computer and the algebraic sum of this integral and the previous ventricular volume was used as the command signal for the volume servopump.

The heart rate was controlled by pacing leads sutured to the left atrium. Coronary perfusion pressure and left ventricular volume and pressure were simultaneously recorded on a strip chart and on a digital magnetic tape with use of a minicomputer (LSI-11) at 5 msec intervals.

**Loading conditions.** Cardiac output of the dog is approximately 100 ml/min/kg body weight. The average weight of the heart-donor dogs was about 20 kg, so that average cardiac output was about 30 ml/sec. The mean arterial pressure of a healthy dog is about 100 mm Hg. Therefore, the total resistance (i.e., \( R_e + R \)) is about 3.3 mm Hg-sec/ml. Since the characteristic impedance is 5% to 10% of the total resistance, we set the normal \( R_e \) value to 0.2 mm Hg sec/ml and the \( R \) value to 3.0 mm Hg-sec/ml. The time constant of diastolic decay of arterial pressure (\( R \times C \) in the three-element model) is about 1.1 sec; therefore, we set the arterial compliance (\( C \)) at 0.4 ml/mm Hg.

Figures 2A through 4B show the changes in wave form caused by the range of the afterload parameter changes tested. Figures 2A, 3A, and 4A show the changes in pressure and volume wave forms as a function of time with 50% to 200% control changes in resistance (figure 2A), compliance (figure 3A), and characteristic impedance (figure 4A). Figures 2B, 3B, and 4B show the corresponding P-V loops.

**Protocol.** Given one of the seven afterload impedances, each ventricle contracted at four end-diastolic volumes and its pressure and volume were recorded into computer memory on-line. Figure 5 shows a representative set of these from P-V loops under a single afterload impedance. A range of preloads were selected so that at the control set of afterload system parameter values (i.e., \( R_e = 0.2 \) mm Hg-sec/ml, \( R = 3.0 \) mm Hg-sec/ml, \( C = 0.4 \) ml/mm Hg) peak systolic pressure would range from 120 to 150 mm Hg, with the highest preload to 50 to 70 mm Hg with the lowest preload. The highest preload was set and after a steady state was reached, beats were recorded (largest loop, figure 5). Then, the preload was decreased stepwise. A similar protocol was repeated with a new set of afterload system parameters by changing one of the components of the three-element model (\( R, C, \) or \( R_e \)) for arterial impedance to 50% or 200% of control, while holding the other two elements constant at their control values. In this way we were able to examine the effects of each element of the impedance model independent of the others. A total of seven sets of afterload parameter combinations were used.
were studied in each of the eight hearts. Values studied for \( R \) were 1.5, 3, and 6 mm Hg-sec/ml, those for \( C \) were 0.2, 0.4, and 0.8 ml/mm Hg, and those for \( R_c \) were 0.1, 0.2, and 0.4 mm Hg-sec/ml. Heart rate was held constant within the protocol but varied from heart to heart between 100 and 140 beats/min.

Data analysis. To obtain the reference ESPVR (ESPVR\(_{\text{REF}}\)) end-systolic P-V points first had to be determined. End-systole was defined as the point in time \( t \) in a given cardiac cycle at which the following ratio of ventricular pressure to volume becomes maximal:

\[
E(t) = \frac{P(t)}{V(t) - V_o}
\]

Since \( V_o \) in this equation was defined as the volume axis intercept of the ESPVR, it was not known until we obtained the ESPVR. Therefore, an iterative procedure was needed to obtain ESPVR\(_{\text{REF}}\). This was done by the computer by first tentatively assuming \( V_o \) to be zero and determining the MPVR point for each loading condition (x’s in figure 5). A least squares linear regression was then applied to these points and a tentative \( V_o \) was calculated as the intercept of this regression line with the volume axis. With use of this \( V_o \) value, the maximum P-V ratio point was recalculated as in the equation above for each loading condition (solid circles in figure 5). On these points a new linear regression was calculated and a new \( V_o \) obtained. This procedure was repeated until \( V_o \) did not change significantly.

In addition to ESPVR\(_{\text{REF}}\), the three following variant of end-systolic P-V relationship were studied: (1) ESPVR\(_{\text{PP-EV}}\), the linear regression of peak pressure on end-ejection volume for each of the four loops, (2) ESPVR\(_{\text{EEP-V}}\), the linear regression of pressure on volume at the time of minimal volume (end-ejection) for each of four loops, and (3) MPVR, the peak value of the ratio of pressure to volume for one of the four preloads, disregarding \( V_o \).

The data recorded on digital magnetic tape were edited, calibrated, and processed on a minicomputer (Data General Eclipse S/120). All linear regressions were done by the method of least squares and both the slope and volume intercept (\( V_o \)) were calculated.

The slope and \( V_o \) data of all the ‘‘ESPVRs’’ were compared with the reference ESPVR data by analysis of variance. Both the slope and volume intercept of the line were analyzed in this way. Values are reported as mean ± SD.

**Results**

Under the control afterload condition, the slope of the ESPVR\(_{\text{REF}}\) averaged 5.3 ± 2.2, with a mean correlation coefficient of .985 ± .011 (\( n = 22 \)). The mean correlation coefficient for all regressions, including all

**FIGURE 3A.** Strip-chart recordings of left ventricular pressure, simulated aortic pressure and left ventricular volume time obtained under three different capacitance values (0.2, 0.4, and 0.8 ml/mm Hg) and constant end-diastolic volume. Abbreviations are as in figure 2A.

**FIGURE 3B.** The left ventricular P-V loops from the same data illustrated in figure 3A. Abbreviations as in figure 2A.
methods and afterload conditions was .980 (n = 207). There was no influence on the correlations of changes in resistance (r = .983, n = 72, p = .21), capacitance (r = .982, n = 72, p = .19), or characteristic impedance (r = .974, n = 63, p = .47). There was, however, a significant difference in r value with the variants of ESPVR (p < .01, n = 69). The average correlation coefficient for ESPVRREF was .988 ± .012, that for ESPVR REF was .971 ± .022, and that for ESPVR REF was .975 ± .028 (p < .01, n = 69).

The average slope and intercept of ESPVR REF under all conditions was 5.17 ± 0.27 (SE) mm Hg/ml and 7.68 ± .68 ml (n = 71). The ESPVR REF line was found to be consistently shifted to the left with a slope of 5.39 ± 0.28 mm Hg/ml and an intercept 7.13 ± 0.73 ml (n = 71, p < .001). ESPVR REF was consistently to the right of the ESPVR REF line, with a slope of 4.91 ± .27 mm Hg/ml and intercept 7.98 ± .66 ml (n = 71, p < .001). An example of the relationship between the ESPVR REF and four MPVR lines (MPVR) is shown in figure 5. The slopes of the MPVR lines were always lower than those of the ESPVR REF lines and varied with the end-systolic pressure.

Table 1 shows the influence of afterload resistance, capacitance, and characteristic impedance on the slope and volume intercepts of alternative ESPVRs. Slopes of each ESPVR were averaged from eight ventricles after being normalized for the reference slope. The difference in volume intercepts between the ESPVR REF and each of the ESPVRs is shown. For ESPVR REF the slope was slightly higher than that for ESPVR REF (p < .0008) and the volume intercept was slightly lower (p < .0002). This difference between slopes and intercepts was influenced by the resistance level (p < .0007 and p < .06, respectively). For the ESPVR REF, method the opposite trend was observed. The slope was slightly lower than that obtained with the reference method (p < .003) and the volume intercept was slightly higher under all resistances (p < .07). These differences were not influenced by the resistance (p = .05).

**FIGURE 4A.** Strip-chart recordings of left ventricular pressure, simulated aortic pressure, and left ventricular volume vs time obtained under three different characteristic impedance values (1, 0.2, and 0.4 mm Hg-sec/ml) and constant end-diastolic volume. Abbreviations as in figure 2A.

**FIGURE 4B.** Left ventricular pressure-volume loops from the same data illustrated in figure 4A. Abbreviations as in figure 2A.
were interested in the comparison between methods under any given set of conditions. There were some spontaneous changes in contractile state during the course of these long experiments. We believe that the difference in the slope of ESPVR_ref under different afterload conditions (table 2) are related to variations in contractile state and not to the influence of afterload condition since, in a previously published study\textsuperscript{27} in which we changed afterload impedance parameters, there was no change in the slope of ESPVR_ref even though there was some increase in V_o with increased afterload resistance.

![Graph](image)

**FIGURE 5.** Comparison of MPVR ignoring V_o (dotted lines) and the ESPVR_ref (solid line). The MPVR varies with each loading condition. The four MPVR points (x's) are used to calculate the ESPVR_ref. The volume-axis intercept (V_o) derived from this first approximation is then used to determine the end-systolic P-V points (solid dots) and a new ESPVR_ref is determined. This iterative process is repeated until V_o does not change (usually only one iteration needed).

For the MPVR method, the slope of the relationship was consistently and significantly (p < .0001) smaller than that for ESPVR_ref, whereas by definition the volume intercept was zero. Because the MPVR method results in individual slopes for each preloaded condition, the numeric results are listed separately in table 2. Preloads were selected so that at the highest preload systolic pressure would range from 120 to 150 mm Hg and from 50 to 70 mm Hg at the lowest preload. For MPVR there were highly significant differences between preloads at all resistance levels (p < .00001) and these differences varied with resistance level (p = .0002).

These data represent normalized values because we

<table>
<thead>
<tr>
<th>Resistance (mm Hg·sec/ml)</th>
<th>( \frac{E_{s}}{E_{s,ref}} )</th>
<th>V_o - V_o_ref (ml)</th>
<th>( \frac{E_{s}}{E_{s,ref}} )</th>
<th>V_o - V_o_ref (ml)</th>
<th>MPVR E_s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>1.1 ± 0.01</td>
<td>-1.1 ± 0.2</td>
<td>0.92 ± 0.03</td>
<td>1.1 ± 0.1</td>
<td>0.58 ± 0.07</td>
</tr>
<tr>
<td>3.0</td>
<td>1.04 ± 0.01</td>
<td>-0.7 ± 0.1</td>
<td>0.94 ± 0.01</td>
<td>0.3 ± 0.2</td>
<td>0.66 ± 0.08</td>
</tr>
<tr>
<td>6.0</td>
<td>1.02 ± 0.01</td>
<td>-0.7 ± 0.2</td>
<td>0.97 ± 0.01</td>
<td>0.5 ± 0.3</td>
<td>0.84 ± 0.07</td>
</tr>
<tr>
<td>Capacitance (ml/mm Hg)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>0.2</td>
<td>1.04 ± 0.01</td>
<td>-0.4 ± 0.1</td>
<td>0.97 ± 0.01</td>
<td>0.6 ± 0.3</td>
<td>0.68 ± 0.04</td>
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<tr>
<td>0.4</td>
<td>1.03 ± 0.01</td>
<td>-0.83 ± 0.2</td>
<td>0.94 ± 0.01</td>
<td>-0.2 ± 0.3</td>
<td>0.74 ± 0.07</td>
</tr>
<tr>
<td>0.8</td>
<td>1.05 ± 0.01</td>
<td>-1.2 ± 0.2</td>
<td>0.94 ± 0.02</td>
<td>0.1 ± 0.2</td>
<td>0.69 ± 0.07</td>
</tr>
<tr>
<td>Characteristic impedance</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg·sec/ml)</td>
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<td></td>
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</tr>
<tr>
<td>0.1</td>
<td>1.03 ± 0.01</td>
<td>-0.2 ± 0.1</td>
<td>0.96 ± 0.01</td>
<td>-0.4 ± 0.4</td>
<td>0.64 ± 0.05</td>
</tr>
<tr>
<td>0.2</td>
<td>1.03 ± 0.01</td>
<td>-1.1 ± 0.1</td>
<td>0.96 ± 0.02</td>
<td>0.35 ± 0.2</td>
<td>0.67 ± 0.07</td>
</tr>
<tr>
<td>0.4</td>
<td>1.09 ± 0.01</td>
<td>-0.8 ± 0.3</td>
<td>0.88 ± 0.04</td>
<td>0.76 ± 0.06</td>
<td></td>
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</tbody>
</table>

Values are means for eight hearts ± SD.

\( E_s \) slope of the ESPVR.
TABLE 2
MPVRs (mm Hg/mC) for six hearts at each of four preloads and nine afterload conditions including three resistances, three capacitances, and three characteristic impedances, and the slope of ESPVRREF

<table>
<thead>
<tr>
<th>Resistance (mm Hg-sec/ml)</th>
</tr>
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<tbody>
<tr>
<td>1.5</td>
</tr>
<tr>
<td>Slope ESPVRREF</td>
</tr>
<tr>
<td>Load 1</td>
</tr>
<tr>
<td>Load 2</td>
</tr>
<tr>
<td>Load 3</td>
</tr>
<tr>
<td>Load 4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Capacitance (ml/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
</tr>
<tr>
<td>ESPVRREF</td>
</tr>
<tr>
<td>Load 1</td>
</tr>
<tr>
<td>Load 2</td>
</tr>
<tr>
<td>Load 3</td>
</tr>
<tr>
<td>Load 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic impedance (mm Hg-sec/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
</tr>
<tr>
<td>ESPVRREF</td>
</tr>
<tr>
<td>Load 1</td>
</tr>
<tr>
<td>Load 2</td>
</tr>
<tr>
<td>Load 3</td>
</tr>
<tr>
<td>Load 4</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
See text for explanation of preload levels 1, 2, 3, 4.
ESPVR slope is significantly different from that of MPVR (p < .001); preload had a significant influence on MPVR (p < .0001).

differences among slopes obtained with the MPVR method (p < .0001).

Contractile state can change the relationship between peak pressure and end-ejection pressure. To examine the possibility that contractile state influences estimates of ESPVR, we examined the relationship between the slope of the ESPVRREF and the difference between ESPVRPP-EVEP or ESPVRFEEP and ESPVRREF for both slope and intercept and found no significant correlation.

Discussion

Our study has shown that within the present experimental conditions the slope of the ESPVR can be approximated quite well by the ESPVRPP-EVEP or ESPVRFEEP over a wide range of afterloaded conditions. The estimation of the ESPVR with a single peak pressure-volume ratio yields poor results because it varies considerably with load.

End-systole, by our definition, does not generally coincide with the time of end-ejection; end-ejection depends on the vascular properties as well as the length of ventricular activation. This is particularly evident in the right ventricle where, because of the high inertness and compliance component of the pulmonary vascular impedance relative to the resistive component, intra-ventricular pressure returns to nearly end-diastolic levels before ejection ceases. Thus, a term is needed that indicates the end of active contraction independent of loading conditions. We have used end-systole as such a term. In practical terms, for most left ventricular contractions, this is very near to the time of the MPVR.

The three alternatives (ESPVRPP-EVEP, ESPVRFEEP, and MPVR) to our definition of ESPVR were selected because of the relative ease with which these measurements can be obtained clinically. The leftward shift from ESPVRREF of ESPVRFEEP is expected, since the peak pressure is always higher than the end-ejection pressure and we shifted the peak pressure to the left to align with end-systolic volume to produce a fictitious P-V point. However, the slope of the relationship was a surprisingly good approximation of that of the ESPVR, being only 3% higher on the average (5.4 vs 5.2 mm Hg/ml). The decrease in volume intercept averaged 10.6% or only 0.8 ml.

ESPVRFEEP consistently shifted rightward from ESPVRREF, with a 4% smaller average slope (5.0 vs 5.2 mm Hg/ml reference) and a very slightly (2.5%) greater volume intercept (2.43 vs 2.37 ml reference). The difference between end-ejection pressure and end-systolic pressure seems to be somewhat load dependent, with a larger percentage difference at higher preloads. This leads to the small slope change and minimal volume intercept shift that was noted.

The difference between the slopes of ESPVRPP-EVEP and/or ESPVRFEEP vs the slope of ESPVRREF appears to be somewhat afterload dependent. As afterload resistance increases, the difference in slope decreased between the ESPVRREF and ESPVRFEEP and between the ESPVRREF and ESPVRPP-EVEP. The explanation for this may be the large difference between peak pressure and end-systolic pressure and between end-ejection pressure and end-systolic pressure at low arterial resistance. This would lead to the larger difference errors in the slope from the ESPVRREF seen at the lower resistances. With changes in capacitance, the greater pressure difference with larger capacitance is accompanied by an increase in the difference between end-systolic and end-ejection volumes. These offsetting trends might explain the lack of any clear difference in the ESPVR parameters with changes in afterload capacitance. With a high characteristic impedance a large
difference was seen between peak pressure and end-systolic pressure. There also was a large difference between end-ejection and end-systolic volumes. This explains the large difference from the slope of ESPVR_ref of both ESPVR_PP-EEV and ESPVR_PP-EVP at this afterload. This result argues against the use of ESPVR_PP-EEV and ESPVR_PP-EVP for the right ventricle because pulmonary arterial characteristic impedance is known to be about three times as large as that of the systemic arteries relative to their resistances.

The results obtained with the P-V ratio alone shows the disadvantage of this technique as opposed to the others. The ratio is clearly load dependent (figure 5, table 2) and significantly smaller than the slope of ESPVR_ref. In addition, a recent study on regional ischemia showed that with ischemia there were large shifts in V_e extrapolated from the physiologic pressure range with little change in slope. Therefore, the relative position of the ESPVR is as important as the slope in indictating ventricular abnormality. V_o is a convenient measure of this relative position. The MPVR, which disregards V_e, is misleading in the assessment of cardiac contractility.

There are several limitations of this study that deserve comment. The loading system used in this isolated heart preparation is a three-element approximation of the much more complex properties of arterial vascular impedance. The impedance modulus spectrum of our simulated vascular properties decay smoothly from the zero-frequency term (resistance) to the high-frequency terms (characteristic impedance), without oscillations that result from pressure wave reflection, and are characteristic of the natural impedance spectrum. These reflected waves could influence the relationship between the peak pressure, end-systolic pressure, and end-ejection pressure and quantitatively change the results found in this study. This possibility needs to be examined further.

The loading conditions tested cover a very wide range of variation in preload and afterload impedance parameters (from one-half to twice normal for each afterload parameter). It is still possible that in some disease states these ranges could be exceeded. With cardiac hypertrophy, for example, contraction is forceful and sustained and it is possible that larger differences between these methods could exist.

There is no agreement as to the use of the term ventricular afterload. We have avoided the issue of whether to consider the arterial input impedance, ventricular pressure, or systolic wall tension or stress as afterload by specifying afterload as the afterload pressure, or the afterload system (impedance). Afterload pressure results from the interaction of the ventricle with the arterial afterload system. When preload (end-diastolic volume) is altered, afterload pressure changes even when the afterload arterial system (impedance) does not.

Each of the individual ESPVRs reported here was obtained from four P-V loops that were obtained by alteration of preload in the face of constant afterload impedance and constant contractile state. These results cannot be applied to the situation in which the preload remains relatively constant and the afterload impedance is pharmacologically manipulated to produce distinct P-V loops for ESPVR. However, most of the time when afterload is changed by drugs or other means, there will be an associated change in preload. How good or poor the approximation of ESPVR_ref by the two alternative methods will be in such a complex situation cannot be predicted from the present results.

Although the ESPVR of isolated hearts has been extensively studied, the application of this approach to the clinical setting is not yet on firm ground. The uncertainty about the accuracy of estimations of end-systolic pressure and volume, along with uncertainty about absence of reflex changes in contractile state while changing loads, have made many investigators skeptical about the accuracy of ESPVR estimation. Furthermore, in animals, the ESPVR is influenced by changes in coronary perfusion, regional ischemia, impedance changes, and probably heart rate. These influencing factors have not detracted from the use of the ESPVR in animals, but to what extent these and other factors are important in patients and to what extent their influence is modified by disease states has yet to be defined. Before the use of the ESPVR can be accepted as a generally applicable index of cardiac contractile state in patients, many more studies will have to be completed. However, since the ESPVR has been shown in animals to be suited for characterizing ventriculovascular coupling, ventricular energetics, and ventricular contractile state, it is likely that it will be applied with increasing frequency in clinical situations.

In conclusion, even though this study revealed statistically significant differences among ESPVR obtained by various methods, the absolute differences are relatively small. Using the ESPVR as we have defined it as the reference, the difference in the slope was less than 5% and that in V_o was less than 0.8 ml for both the ESPVR_PP-EEV and ESPVR_PP-EVP methods. In view of the magnitude of error involved in the clinical determination of ventricular volume, use of both ESPVR_PP-EEV and ESPVR_PP-EVP can be considered reasonably good
methods to estimate the slope and $V_o$ of ESPVR in patients. At present, however, this conclusion is valid only for the normal ventricle, in which the preload is changed in the presence of relatively stable afterload impedance and constant contractility.

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